

P A T E N T C O O P E R A T I O N T R E A T Y

PCT

NOTIFICATION OF ELECTION

(PCT Rule 61.2)

From the INTERNATIONAL BUREAU

To:

Commissioner
 US Department of Commerce
 United States Patent and Trademark
 Office, PCT
 2011 South Clark Place Room
 CP2/5C24
 Arlington, VA 22202
 ETATS-UNIS D'AMERIQUE
 in its capacity as elected Office

Date of mailing (day/month/year) 25 June 2001 (25.06.01)	
International application No. PCT/US00/21225	Applicant's or agent's file reference 15185/126708
International filing date (day/month/year) 03 August 2000 (03.08.00)	Priority date (day/month/year) 03 August 1999 (03.08.99)
Applicant ANDERSSON, Carl, M. et al	

1. The designated Office is hereby notified of its election made:

☒ in the demand filed with the International Preliminary Examining Authority on:
 27 February 2001 (27.02.01)

☐ in a notice effecting later election filed with the International Bureau on:

2. The election ☒ was

☐ was not

made before the expiration of 19 months from the priority date or, where Rule 32 applies, within the time limit under Rule 32.2(b).

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No.: (41-22) 740.14.35	Authorized officer Charlotte ENGER Telephone No.: (41-22) 338.83.38
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INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference 15185/126708	FOR FURTHER ACTION see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.	
International application No. PCT/US 00/ 21225	International filing date (day/month/year) 03/08/2000	(Earliest) Priority Date (day/month/year) 03/08/1999
Applicant ACADIA PHARMACEUTICALS, INC. et al.		

This International Search Report has been prepared by this International Searching Authority and is transmitted to the applicant according to Article 18. A copy is being transmitted to the International Bureau.

This International Search Report consists of a total of 3 sheets.
☒ It is also accompanied by a copy of each prior art document cited in this report.

1. Basis of the report

- a. With regard to the **language**, the international search was carried out on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.

☐ the international search was carried out on the basis of a translation of the international application furnished to this Authority (Rule 23.1(b)).

- b. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international search was carried out on the basis of the sequence listing:

☐ contained in the international application in written form.

☐ filed together with the international application in computer readable form.

☐ furnished subsequently to this Authority in written form.

☐ furnished subsequently to this Authority in computer readable form.

☐ the statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.

☐ the statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished

2. ☐ **Certain claims were found unsearchable** (See Box I).

3. ☐ **Unity of invention is lacking** (see Box II).

4. With regard to the **title**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established by this Authority to read as follows:

5. With regard to the **abstract**,

☒ the text is approved as submitted by the applicant.

☐ the text has been established, according to Rule 38.2(b), by this Authority as it appears in Box III. The applicant may, within one month from the date of mailing of this international search report, submit comments to this Authority.

6. The figure of the **drawings** to be published with the abstract is Figure No.

☐ as suggested by the applicant.

☐ because the applicant failed to suggest a figure.

☐ because this figure better characterizes the invention.

☒ None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No

/US 00/21225

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C209/40 C07B61/00 C07C213/02 C07C213/08 C07C249/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category °	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 09073 A (AKZO NOBEL) 25 February 1999 (1999-02-25) claims 1,10; examples ---	1, 19
A	WO 98 29376 A (RHONE-POULENC RORER) 9 July 1998 (1998-07-09) page 8, line 21 -page 9, line 15; claims 40-45 ----- -/--	1, 19



Further documents are listed in the continuation of box C.



Patent family members are listed in annex.

° Special categories of cited documents :

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

9 November 2000

Date of mailing of the international search report

01/12/2000

Name and mailing address of the ISA

European Patent Office, P.B. 5818 Patentlaan 2
NL - 2280 HV Rijswijk
Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,
Fax: (+31-70) 340-3016

Authorized officer

Zervas, B

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>JOSEPH M. SALVINO ET AL.: "Parallel Synthesis of Aldehydes and Ketone Facilitated by a New Solid-Phase Weinreb Amide" JOURNAL OF ORGANIC CHEMISTRY., vol. 64, no. 6, 19 March 1999 (1999-03-19), pages 1823-1830, XP002152402 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 cited in the application page 1824, column 1, line 1 -page 1827, column 2, line 26</p> <p>---</p>	1,19
A	<p>ANGELO LIGUORI ET AL.: "Novel Approach to the Ring-Opening Reaction of Isoxazolidinium Salts to 1,3-Amino Alcohols" CHEMISCHE BERICHTE, vol. 121, 1988, pages 105-109, XP002152403 WEINHEIM DE cited in the application page 105, column 1, line 1 -page 106, column 2, line 18</p> <p>---</p>	1,19
A	<p>ERIC E. SWAYZE ET AL.: "The Synthesis of N,N'-O-Trisubstituted Hydroxylamines via a Mild Reductive Alkylation Procedure: An Improved Synthesis of the MMI Backbone" SYNLETT., no. 7, July 1997 (1997-07), pages 859-861, XP002152404 THIEME VERLAG, STUTTGART., DE ISSN: 0936-5214 cited in the application the whole document</p> <p>-----</p>	1,19

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No

US 00/21225

Patent document cited in search report		Publication date	Patent family member(s)		Publication date
WO 9909073	A	25-02-1999	AU	9344898 A	08-03-1999
WO 9829376	A	09-07-1998	AU	5719998 A	31-07-1998
			BG	103501 A	31-03-2000
			BR	9713773 A	21-03-2000
			CZ	9902208 A	17-11-1999
			EP	0946478 A	06-10-1999
			NO	992896 A	13-08-1999
			PL	334196 A	14-02-2000
			US	6133409 A	17-10-2000
			ZA	9711453 A	14-09-1998

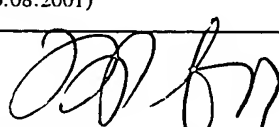
PATENT COOPERATION TREATY

PCT

REG'D 09 OCT 2001

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15185/126708	FOR FURTHER ACTION		See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US00/21225	International filing date (day/month/year) 03 August 2000 (03.08.2000)	Priority date (day/month/year) 03 August 1999 (03.08.1999)	
International Patent Classification (IPC) or national classification and IPC IPC(7): C07C 211/00 and US Cl.: 564/384			
Applicant ACADIA PHARMACEUTICALS, INC.			
<p>1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of <u>3</u> sheets, including this cover sheet.</p> <p><input type="checkbox"/> This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).</p> <p>These annexes consist of a total of <u> </u> sheets.</p> <p>3. This report contains indications relating to the following items:</p> <ul style="list-style-type: none"> I <input checked="" type="checkbox"/> Basis of the report II <input type="checkbox"/> Priority III <input type="checkbox"/> Non-establishment of report with regard to novelty, inventive step and industrial applicability IV <input type="checkbox"/> Lack of unity of invention V <input checked="" type="checkbox"/> Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement VI <input type="checkbox"/> Certain documents cited VII <input type="checkbox"/> Certain defects in the international application VIII <input type="checkbox"/> Certain observations on the international application 			
Date of submission of the demand 27 February 2001 (02.02.2001)		Date of completion of this report 06 August 2001 (06.08.2001)	
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230		Authorized officer Samuel A Barts  Telephone No. 703-308-1235	

Form PCT/IPEA/409 (cover sheet) (July 1998)

I. Basis of the report**1. With regard to the elements of the international application:***

- ☒ the international application as originally filed.
- ☒ the description:
pages 1-10 as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the claims:
pages 11-16, as originally filed
pages NONE, as amended (together with any statement) under Article 19
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☒ the drawings:
pages 1-3, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____
- ☐ the sequence listing part of the description:
pages NONE, as originally filed
pages NONE, filed with the demand
pages NONE, filed with the letter of _____

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☒ The amendments have resulted in the cancellation of:

- ☒ the description, pages none
- ☒ the claims, Nos. none
- ☒ the drawings, sheets/~~fig~~ none

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Application No.

PCT/US00/21225

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims <u>1-34</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1-34</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1-34</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Claims 1-34 meet the industrial applicability as defined by PCT Article 33(4). The claim produces amines that have a variety of uses such as being a reactant to make emulsifier and germicides.

Claims 1-34 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the preparation of tertiary amines comprising sequential, exhaustive alkylation of a hydroxylamine derivatives and the cleavage of the O-N bond.

----- NEW CITATIONS -----

NONE

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

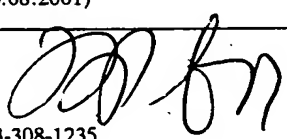
(PCT Article 36 and Rule 70)

Applicant's or agent's file reference 15185/126708	FOR FURTHER ACTION See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)	
International application No. PCT/US00/21225	International filing date (day/month/year) 03 August 2000 (03.08.2000)	Priority date (day/month/year) 03 August 1999 (03.08.1999)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07C 211/00 and US Cl.: 564/384		
Applicant ACADIA PHARMACEUTICALS, INC.		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.
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These annexes consist of a total of ___ sheets.

3. This report contains indications relating to the following items:
 - I ☒ Basis of the report
 - II ☐ Priority
 - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
 - IV ☐ Lack of unity of invention
 - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
 - VI ☐ Certain documents cited
 - VII ☐ Certain defects in the international application
 - VIII ☐ Certain observations on the international application

Date of submission of the demand 27 February 2001 (02.02.2001)	Date of completion of this report 06 August 2001 (06.08.2001)
Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Samuel A Barts  Telephone No. 703-308-1235

Form PCT/IPEA/409 (cover sheet)(July 1998)

I. Basis of the report**1. With regard to the elements of the international application:***☒ the international application as originally filed.☒ the description:pages 1-10 as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____☒ the claims:pages 11-16 as originally filedpages NONE, as amended (together with any statement) under Article 19pages NONE, filed with the demandpages NONE, filed with the letter of _____☒ the drawings:pages 1-3 as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____☐ the sequence listing part of the description:pages NONE as originally filedpages NONE, filed with the demandpages NONE, filed with the letter of _____**2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.**

These elements were available or furnished to this Authority in the following language _____ which is:

☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).☐ the language of publication of the international application (under Rule 48.3(b)).☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).**3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:**☐ contained in the international application in printed form.☐ filed together with the international application in computer readable form.☐ furnished subsequently to this Authority in written form.☐ furnished subsequently to this Authority in computer readable form.☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.**4. ☒ The amendments have resulted in the cancellation of:**☒ the description, pages none☒ the claims, Nos. none☒ the drawings, sheets/fig none**5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).****

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).

** Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International Publication No.

PCT/US00/21225

V. Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement**1. STATEMENT**

Novelty (N)	Claims <u>1-34</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>1-34</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>1-34</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS (Rule 70.7)

Claims 1-34 meet the industrial applicability as defined by PCT Article 33(4). The claim produces amines that have a variety of uses such as being a reactant to make emulsifier and germicides.

Claims 1-34 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the preparation of tertiary amines comprising sequential, exhaustive alkylation of a hydroxylamine derivatives and the cleavage of the O-N bond.

----- NEW CITATIONS -----
NONE

(19) World Intellectual Property Organization
International Bureau



(43) International Publication Date
8 February 2001 (08.02.2001)

PCT

(10) International Publication Number
WO 01/09081 A1

(51) International Patent Classification⁷: C07C 209/40, C07B 61/00, C07C 213/02, 213/08, 249/08

(21) International Application Number: PCT/US00/21225

(22) International Filing Date: 3 August 2000 (03.08.2000)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/146,978 3 August 1999 (03.08.1999) US

(71) Applicant (for all designated States except US): ACADIA PHARMACEUTICALS, INC. [US/US]; 3911 Sorento Valley Boulevard, San Diego, CA 92121 (US).

(72) Inventors; and

(75) Inventors/Applicants (for US only): ANDERSSON, Carl, M. [SE/DK]; Dahlvangvej 81.2 MF, DK-2600 Glostrup (DK). GUSTAFSSON, Magnus [SE/SE]; Kung Oskars vag 9A, S-222 40 Lund (SE). OLSSON, Kent, Roger, I. [SE/SE]; Andreegatan 8, S-211 49 Malmö (SE).

(74) Agents: MCPAUL, Georgina, M. et al.; Pillsbury Madison & Sutro LLP, 50 Fremont Street, San Francisco, CA 94105 (US).

(81) Designated States (national): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CR, CU, CZ, DE, DK, DM, DZ, EE, ES, FI, GB, GD, GE, GH, GM, HR, HU, ID, IL, IN, IS, JP, KE, KG, KP, KR, KZ, LC, LK, LR, LS, LT, LU, LV, MA, MD, MG, MK, MN, MW, MX, MZ, NO, NZ, PL, PT, RO, RU, SD, SE, SG, SI, SK, SL, TJ, TM, TR, TT, TZ, UA, UG, US, UZ, VN, YU, ZA, ZW.

(84) Designated States (regional): ARIPO patent (GH, GM, KE, LS, MW, MZ, SD, SL, SZ, TZ, UG, ZW), Eurasian patent (AM, AZ, BY, KG, KZ, MD, RU, TJ, TM), European patent (AT, BE, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GW, ML, MR, NE, SN, TD, TG).

Published:

- With international search report.
- Before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments.

For two-letter codes and other abbreviations, refer to the "Guidance Notes on Codes and Abbreviations" appearing at the beginning of each regular issue of the PCT Gazette.

(54) Title: SOLID PHASE PARALLEL SYNTHESIS OF TERTIARY AMINES

(57) Abstract: Described is method for preparing tertiary amines comprising sequential, exhaustive alkylation of a hydroxylamine derivative and cleavage of the O-N bond using the following steps: (a) reacting the hydroxylamine derivative with an alkylating agent or with a carbonyl compound to form an oxime intermediate; (b) reacting the oxime intermediate with a reducing agent to produce an alkylated derivative; (c) reacting the alkylated derivative with an alkylating agent or a carbonyl compound in the presence of a reducing agent to produce a dialkylated derivative; (d) reacting the dialkylated derivative with an alkylating agent to produce a quaternized derivative; (e) reacting the quaternized derivative with a reagent causing cleavage of the O-N bond to produce a tertiary amine.

WO 01/09081 A1

Solid Phase Parallel Synthesis of Tertiary Amines

This application claims priority from U.S. Provisional Application 60/146,978, filed August 3, 1999, which application is incorporated herein by reference.

Field of the Invention

- 5 The present invention relates to the synthesis of tertiary amines. More particularly a method of solid phase tertiary amine synthesis through sequential, exhaustive alkylation of a hydroxylamine derivative and cleavage of the N-O bond is described.

Background of the Invention

- 10 Solid phase organic synthesis (SPOS) offers considerable advantages compared to traditional solution phase reactions. In particular, solid phase reactions are very attractive for combinatorial and parallel work because of the relative ease of purification of the resin bound material after each reaction step. Purification can be performed by simple washing and filtration. (see e.g., Obrecht and Villalgordo: Solid-Supported Combinatorial and Parallel Synthesis of Small-Molecular-Weight Compound Libraries, Pergamon, 1998).

- 15 Since virtually every endogenous and synthetic ligand that interacts with receptors in the central nervous system contains a basic functionality, most often a tertiary or secondary amino group, SPOS methods for the preparation of such compounds remains an extremely important aspect of medicinal chemistry aimed at central nervous system active drugs.

- 20 The solid phase organic synthesis of tertiary amines, using the nitrogen as the point of attachment to the solid support, is known in the art. (See Figure 1) However, the methods

described in previous work have disadvantages related to the lability of the linkers used as well as the release reactions.

Summary of the Invention.

Described is a new method for the solid phase synthesis of amines which comprises the linkage of an amino group via an N-O bond from resin-(linker)-O-NH₂. A series of reliable reactions are used for the introduction of all three R groups of the tertiary amine NR¹R²R³ (forming resin-(linker) O-N⁺R¹R²R³). Finally, a novel release reaction, which delivers exclusively the material that has successfully undergone each of the previous synthetic steps, is performed. (Resin-linker-O-N⁺R¹R²R³ gives N R¹R²R³). This type of release reaction, conditional release, serves to provide very pure product without any need for purification. The protocol is equally adaptable to split synthesis or linear parallel synthesis.

Brief Description of the Drawings

The present invention may be better understood by reference to the appended figures and specification.

Figure 1 illustrates the prior art conditional release reaction.

Figure 2 illustrates the prior art alkylation reaction using alkoxyamine.

Figure 3 illustrates alkoxyammonium ion cleavage

Figure 4 illustrates alkoxyammonium ion reactivity in the prior art.

Figure 5 illustrates reductive alkylation and alkylation as used in the prior art.

Figure 6 illustrates the formation of a hydroxylamine resin

Figure 7 illustrates the entire process of the presently described method.

Figure 8 illustrates the novel conditional release reaction.

Detailed Description of the Invention.

Hydroxylamine resin may be prepared according to Salvino et al., or by attachment of a
5 suitably protected hydroxylamine derivative to the desired resin, e. g. chloromethylated
polystyrene or polystyrene grafted or functionalized with a suitable linker.

Introduction of the first R-group to the hydroxylamine resin is achieved either via
alkylation or oxime formation followed by reduction. R may be any organyl group. More
preferably R can be any cyclic, aromatic or acyclic organyl group

10 Alkylation is performed by reacting the hydroxylamine derivative with an alkylating agent.
Suitable alkylating agents are compounds carrying a nucleofuge such as organyl halides,
tosylates or the like. In general alkylating agents may have the formula R-LG, wherein R
is an organyl and LG is a nucleofuge

In an alternative to alkylation, oxime formation can be run in one pot or the oxime may be
15 isolated. Aromatic groups may be introduced, e.g., via palladium-catalyzed coupling
between the resin and an aromatic or heteroaromatic halide or triflate. Any ketone or
aldehyde serves to form an oxime with the resin. Many reducing agents can be used to
reduce the oxime to the N-substituted hydroxylamine, including aluminum or boron
complex hydrides.

20 The second R-group may again be any organyl group, and may be introduced via alkylation
as described above. Alternately reductive amination may be used to introduce the second
R group, wherein any aldehyde or ketone together with a suitable reducing agent is used.

The resin bound N,N-dialkylhydroxylamine derivative so obtained may be alkylated with any organic compound carrying a suitable nucleofuge, such as triflate, halide or tosylate, to form the cationic alkoxyammonium intermediate. This step introduces the third R-group.

Every step in the above sequence is easily driven to completion by the use of excess

5 reagents and reactants and subsequent washing of the resin bound intermediate. Very high selectivity for the introduction of precisely one organyl group in each step (avoiding dialkylation) is achieved particularly effectively by performing oxime formation for the introduction of the first R-group, reduction, reductive amination for the introduction of the second R-group and alkylation for the introduction of the third R-group. This sequence of
10 steps is preferred.

Extremely mild and exclusively conditional release is performed by treating the alkoxyammonium resin which has resulted from the above listed steps, with lithium iodide, preferably at elevated temperature. This reaction has been previously performed in solution by Liguori et al. However, the application of this very mild method for cleaving
15 the N-O bond and thus releasing the desired organic product from the polymer support is novel, and serves to release selectively only material that has reacted in all the previous steps.

Furthermore, this method of release is tolerant to the presence of virtually any substituent in the product amine, since only modest temperatures and neutral conditions are used.

20 Removal of the reagent lithium iodide can be performed by liquid-liquid or liquid-solid extraction, optionally in combination with further purification of the organic product $\text{NR}^n\text{Alk}^1\text{Alk}^2$ via capture on acidic ion exchange resin, washing, and release as has been described by others. It is noticeable that this new linking strategy shows unprecedented selectivity for the release of only desired material, allows very mild conditions for

assembly and cleavage of the amines and does not leave any compulsory functionality in the product; hence the linking is traceless.

The term organyl is used to denote any acyclic, alicyclic or heterocyclic, alkyl, alkenyl or alkynyl group, or an aromatic or heteroaromatic group. These groups may be branched or unbranched and may be optionally substituted with heteroatom-containing fragments, connected through either a heteroatom or a carbon atom.

A preferred embodiment of the inventive method disclosed comprises the following steps.

Initially the hydroxylamine derivative PONH_2 is reacted with an alkylating agent having the formula R-LG or with a carbonyl compound having the formula RCOR' to form an

oxime intermediate having the formula $\text{PON}=\text{CR}'\text{R}$. Most preferably the hydroxylamine derivative is reacted with a aldehyde or ketone. The resulting oxime intermediate is

reacted with a reducing agent to produce an alkylated derivative, having the formula $\text{PONH}(\text{Alk}^1)$. The alkylated derivative is reacted with an alkylating agent having the

formula R-LG or a carbonyl compound having the formula RCOR' in the presence of a

reducing agent to produce a dialkylated derivative having the formula $\text{PON}(\text{Alk}^1)(\text{Alk}^2)$.

Most preferably the alkylated derivative is reacted with a carbonyl compound. Even more preferably the carbonyl compound is an aldehyde or a ketone. The resultant dialkylated

derivative is reacted with an alkylating agent having the formula $\text{R}''\text{-X}$ to produce a

quaternized derivative, having the formula $\text{PON}^+\text{R}''(\text{Alk}^1)(\text{Alk}^2)$. Finally the quaternized

derivative is reacted with a reagent which causes cleavage of the O-N bond to produce a tertiary amine having the formula $\text{NR}''(\text{Alk}^1)(\text{Alk}^2)$. In this preferred embodiment of the

method P is an organyl group or solid support, R is an organyl group, LG is a nucleofuge,

R' is an organyl group or hydrogen, X is a nucleofuge, R'' is an organyl group and Alk^1 and

Alk² are the same or different and are each independently selected from the group consisting of R and CHRR'.

Examples

- 5 The examples given below are not intended to be limiting. Several modifications to the procedures described below are possible. The scope of the invention is limited by the appended claims only.

Examples are given below for the preparation of tertiary amines according to the method of
10 the invention. The stepwise procedure is best exemplified by examples where the hydroxylamine derivative is soluble, i.e. P of the starting PONH₂ is an organyl group, since intermediates may be characterized in this case. In the solution phase examples below, P is benzyl. In the solid phase examples below, P is a modified Wang ., Argogel, or Merrifield resin. During the latter experiments, reaction progress was monitored by solid-phase or gel-
15 phase IR spectroscopy.

The methods and reagents employed for cleavage of the quaternized substrates PON⁺R₃ are anticipated in the prior art, particularly in Liguori et. al. Chem. Ber. 1988, 121, 105-109 and in Liguori et. al. Tetrahedron 1984, 40, 1901-1906 and references cited therein.

- 20 Methods for conducting other steps of the invention were also previously described in the art, for example in Swayze et. al. Synlett 1997, 859, Cannon et. al. J. Med. Chem. 1973, 16, 287, and Kano et. al. Tetrahedron 1992, 48, 10075, which discuss reductive aminations of relevance to the present invention, and in Salvino et. al. J. Org. Chem. 1999, 64, 1823 and Floyd et. al. Tetrahedron Lett. 1996, 37, 8045-8048 which both describe suitably modified
25 resins. However, none of these procedures have been employed for the multi-step parallel

preparation of tertiary amines, which is the subject matter disclosed in the present application.

Analysis of reaction products was performed using LC-MS and NMR spectroscopy. For LC-MS analyses, a HP 1100 LC-MSD system equipped with a binary pump and diode array detector was used. Mass spectral data were collected using an electrospray interface at positive mode, scanning from mass 80 to mass 700. The column was a Luna C18, 3 micrometer particle size, measuring 4.6x75 mm. A Phenomenex C18 4x3 mm guard column was used. The mobile phase consisted of A: 50% 8mM ammoniumacetate / 50% acetonitrile and B: 5% 8 mM ammoniumacetate / 95% acetonitrile. A gradient program: 44.5% B at time 0 min increasing linearly to 100% B at time 11 min was used. The flowrate was 0.6 ml/min. Rt indicates retention times for the products under these experimental condition. NMR spectra were recorded on a 400 MHz apparatus.

15 Solution phase experiments (P = benzyl):

Example 1: Step (a), introduction of (Alk¹)

Synthesis of O-(Benzyl)benzaldoxime(I)

A solution of O-(benzyl)hydroxylamine (1 eq.), benzaldehyde (1 eq.) and acetic acid (5% v/v in MeOH) was stirred for 15 h at rt. Aqueous workup and column chromatography gave I as a colorless oil. The product was identified using NMR spectroscopy, e.g. a peak at 8.18ppm (singlet, HC=N) was diagnostic.

Example 2: Step (b), introduction of (Alk¹)

25 *Synthesis of N-Benzyl-O-(benzyl)hydroxylamine (II)*

To a solution of I (1 eq.) and $\text{BH}_3(\text{pyridine})$ (4 eq.) in methanol was added HCl in dioxane (excess). The reaction mixture was stirred at rt for 12 h. Aqueous basic workup and column chromatography afforded II as a colorless oil. LC-MS: $R_t = 5.1$ min.

5 Example 3: Step (c), introduction of (Alk^2)

Synthesis of N-Isobutyl-N,O-dibenzylhydroxylamine (III)

To a solution of II (1 eq.), 2-methylpropanal (1 eq.) and $\text{BH}_3(\text{pyridine})$ (1 eq.) in THF:MeOH (1:3) was added PPTS (1 eq.). The reaction mixture was stirred at rt for 12 h and afforded, after aqueous workup and purification by column chromatography, III as a
10 colorless oil.

LC-MS: $R_t = 11.3$ min.

Example 4: Step (d), introduction of (R''')

Quaternization of III to give IV

15 To a solution of III (1 eq.) in CH_2Cl_2 was added Na_2CO_3 (excess) and MeOTf (5 eq.). The reaction mixture was stirred at rt for 15 h. Evaporation of excess MeOTf and CH_2Cl_2 afforded a mixture of Na_2CO_3 and IV. Extraction with EtOH afforded the product as a white solid after evaporation.

Analysis by NMR confirmed the identity of the product, e. g. a diagnostic peak at 3.6 ppm
20 (singlet, N^+Me)

Similar reactions excluding Na_2CO_3 were also effective.

Example 5: Step (e), cleavage

Synthesis of N-Benzyl-N-isobutyl-N-methylamine (V)

To a solution of IV in dioxane or MeCN was added LiI (2 eq.). The reaction mixture was heated for 12 h at 70° C. Aqueous workup and purification through an ion exchange column (Isolute SCX) afforded V. LC-MS: Rt = 5.8 min.

Similar cleavages of compound IV were effected using Et₃N in CH₂Cl₂, K₂CO₃ in DMF or
5 SmI₂ in THF.

Solid phase experiments (P = solid support):

Synthesis of a hydroxylamine substrate PONH₂ (P = solid support) from Argogel resin was conducted in analogy with the procedure in Salvino et. al. J. Org. Chem. 1999, 64, 1823,
10 which provided the required polystyrene-polyethylene glycol-ONH₂ resin (VI).

Example 6: Step (a), introduction of (Alk¹)

Oxime resin (VII)

Resin VI was swollen in THF:MeOH (2:1) for 5 min. Cyclohexylcarboxaldehyde (excess)
15 and HOAc were added. The mixture was stirred at rt for 150 h. The resin was filtered and washed with THF and MeOH followed by drying at 40 °C under vacuo.

Example 7: Step (a), introduction of (Alk¹)

Hydroxylamine resin (VIII)

20 To oxime resin VII in THF:MeOH (1:1) were added BH₃(pyridine) and HCl in dioxane (both in excess). The reaction mixture was shaken at rt for 15 h, filtered and washed with Et₃N in MeOH and then MeOH and finally dried in vacuo

Example 8: Step (b), introduction of (Alk²)

25 *Hydroxylamine resin (IX)*

To resin VIII in THF:MeOH (3:1) was added 2-methylpropanal (excess), BH_3 (pyridine) (excess) and PPTS (excess). The reaction mixture was shaken at rt for 12 h, filtered and washed with MeOH and THF followed by drying under vacuo.

5 Example 9: Step (c), introduction of (R")

Quaternization of hydroxylamine resin IX

To resin IX in CH_2Cl_2 was added MeOTf (excess). The reaction mixture was shaken at rt for 12 h, filtered, washed with CH_2Cl_2 and dried under vacuo to provide the quaternized resin X.

10

Example 10: Step (d), cleavage

Preparation of N-Cyclohexylmethyl-N-isobutyl-N-methylamine

Quaternized resin X, prepared above, when subjected to any of the conditions given in Example 5 above, released the desired amine, N-Cyclohexylmethyl-N-isobutyl-N-

15 methylamine.

We claim

1. A method for preparing tertiary amines comprising:

5 sequential, exhaustive alkylation of a hydroxylamine derivative; and,
cleavage of the O-N bond.

2. The method of claim 1 wherein the sequential, exhaustive alkylation of a
hydroxylamine derivative of the formula PONH_2 comprises the steps of:

10 a) forming an alkylated derivative, having the formula $\text{PONH}(\text{Alk}^1)$, by reacting the
hydroxylamine derivative with

an alkylating agent having the formula R-X ,

or a carbonyl compound having the formula RCOR' to form an oxime

intermediate having the formula $\text{PON}=\text{CR}'\text{R}$ and reacting the oxime intermediate

15 with a reducing agent;

b) forming a dialkylated derivative having the formula $\text{PON}(\text{Alk}^1)(\text{Alk}^2)$ by
reacting the alkylated derivative with

an alkylating agent having the formula R-LG ,

or a carbonyl compound having the formula RCOR' in the presence of a

20 reducing agent; and,

c) reacting the dialkylated derivative with an alkylating agent having the formula
 $\text{R}''\text{-X}'$ to produce a quaternized derivative, having the formula $\text{PON}^+\text{R}''(\text{Alk}^1)(\text{Alk}^2)$,
wherein P is an organyl group or solid support, R is an organyl group, R' is an organyl
group or hydrogen, R'' is an organyl group, X and X' are each a nucleofuge, and Alk^1 and

Alk² are the same or different and are each independently selected from the group consisting of R and CHRR'.

3. The method of claim 2 wherein P is a solid support.

5

4. The method of claim 2 wherein P is grafted or functionalized polystyrene.

5. The method of claim 2 wherein P is selected from the group consisting of Wang resin, Argogel resin, Merrifield resin and Tentagel resin.

10

6. The method of claim 2, wherein P is benzyl.

7. The method of claim 2 wherein the alkylating agents are selected from the group consisting of primary organyl chloride, bromide, iodide, tosylate, mesylate and triflate.

15

8. The method of claim 2 wherein the reducing agent is a complex hydride reagent.

9. The method of claim 8 wherein the reducing agent is applied under acidic conditions.

20

10. The method of claim 2 wherein the reducing agent is selected from the group consisting of BH₃(pyridine), NaCNBH₃, NaBH₄, Na(OAc)₃BH, Zn(BH₄)₂, and B₂H₆.

11. The method of claim 2 where X is triflate.

25

12. The method of claim 2 wherein step b) is performed using a carbonyl compound and wherein the carbonyl compound is an aldehyde or ketone.
13. The method of claim 2 wherein step d) is performed using a bifunctional reagent,
5 such that R" and (Alk²) of the quaternized derivative form a ring.
14. The method of claim 13 wherein the ring contains 4, 5, or 6 carbon atoms.
15. The method described in claim 1, wherein the sequential, exhaustive alkylation of a
10 hydroxylamine derivative produces a quaternized derivative having the formula $\text{PON}^+\text{R}''(\text{Alk}^1)(\text{Alk}^2)$, and wherein cleavage of the O-N bond comprises reacting the quaternized derivative with a reagent causing cleavage of the O-N bond to produce a tertiary amine having the formula $\text{NR}''(\text{Alk}^1)(\text{Alk}^2)$ where R" is an organyl and Alk¹ and Alk² are the same or different and are each independently selected from the group
15 consisting of R and CHRR'.
16. The method of claim 15 wherein the reagent is iodide ion or a base.
17. The method of claim 15 wherein the reagent is samarium iodide or lithium iodide.
20
18. The method of claim 15 wherein the reagent is a trialkyl amine or carbonate.
19. A method for preparing tertiary amines comprising:
a) forming an alkylated derivative, having the formula $\text{PONH}(\text{Alk}^1)$, by reacting the
25 hydroxylamine derivative with

an alkylating agent having the formula R-X,

or a carbonyl compound having the formula RCOR' to form an oxime

intermediate having the formula $\text{PON}=\text{CR}'\text{R}$ and reacting the oxime intermediate

with a reducing agent;

- 5 b) forming a dialkylated derivative having the formula $\text{PON}(\text{Alk}^1)(\text{Alk}^2)$ by reacting the alkylated derivative with

an alkylating agent having the formula R-LG,

or a carbonyl compound having the formula RCOR' in the presence of a reducing agent; and,

- 10 c) reacting the dialkylated derivative with an alkylating agent having the formula $\text{R}''\text{-X}'$ to produce a quaternized derivative, having the formula $\text{PON}^+\text{R}''(\text{Alk}^1)(\text{Alk}^2)$; and,

d) reacting the quaternized derivative with a reagent causing cleavage of the O-N bond to produce a tertiary amine having the formula $\text{NR}''(\text{Alk}^1)(\text{Alk}^2)$;

wherein P is an organyl group or solid support, R is an organyl group, R' is an organyl

- 15 group or hydrogen, R'' is an organyl group, X and X' are the same or different and are each a nucleofuge, and Alk^1 and Alk^2 are the same or different and are each independently selected from the group consisting of R and CHRR' .

20. The method of claim 19 wherein P is grafted or functionalized polystyrene, the
20 hydroxylamine derivative is reacted with a carbonyl compound and the alkylated derivative is reacted with a carbonyl compound, the reducing agent is $\text{BH}_3(\text{pyridine})$, NaCNBH_3 , or $\text{Na}(\text{OAc})_3\text{BH}$, R'' is a methyl group, X is triflate, and the reagent is iodide ion or a base.

21. The method of claim 19 wherein P is a solid support.

25

22. The method of claim 19 wherein P is grafted or functionalized polystyrene.

23. The method of claim 19 wherein P is selected from the group consisting of Wang resin, Argogel resin, Merrifield resin and Tentagel resin.

5

24. The method of claim 19 wherein P is benzyl.

25. The method of claim 19 wherein the alkylating agents are selected from the group consisting of primary organyl chloride, bromide, iodide, tosylate, mesylate and triflate.

10

26. The method of claim 19 wherein the reducing agent is a complex hydride reagent.

27. The method of claim 26 wherein the reducing agent is applied under acidic conditions.

15

28. The method of claim 19 wherein the reducing agent is selected from the group consisting of $\text{BH}_3(\text{pyridine})$, NaCNBH_3 , NaBH_4 , $\text{Na}(\text{OAc})_3\text{BH}$, $\text{Zn}(\text{BH}_4)_2$, and B_2H_6 .

29. The method of claim 19 where X is triflate.

20

30. The method of claim 19 wherein step d) is performed using a bifunctional reagent, such that R'' and (Alk^2) of the quaternized derivative form a ring.

31. The method of claim 30 wherein the ring contains 4, 5, or 6 carbon atoms.

25

32. The method of claim 19 wherein the reagent is iodide ion or a base.
33. The method of claim 19 wherein the reagent is samarium iodide or lithium iodide.
- 5 34. The method of claim 19 wherein the reagent is a trialkyl amine or carbonate.

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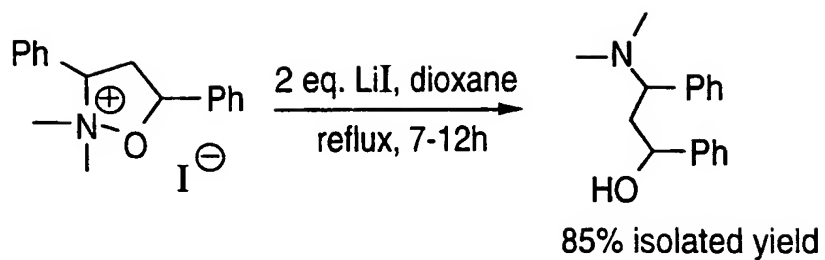


FIG. 1

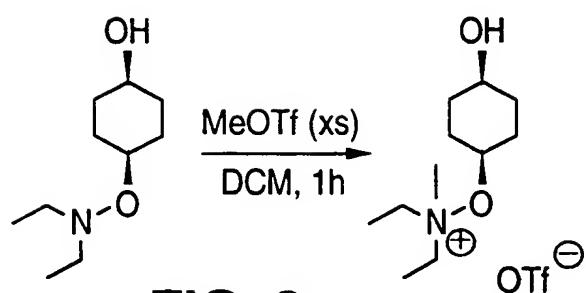


FIG. 2a

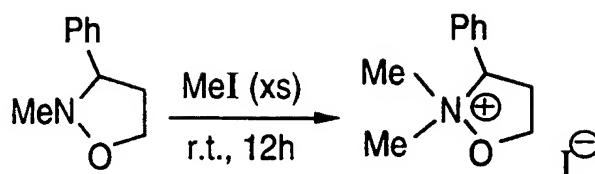


FIG. 2b

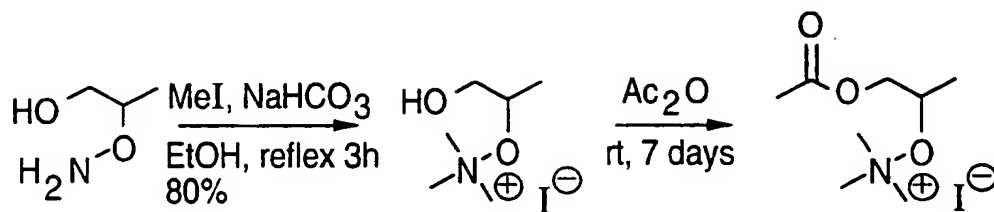


FIG. 2c

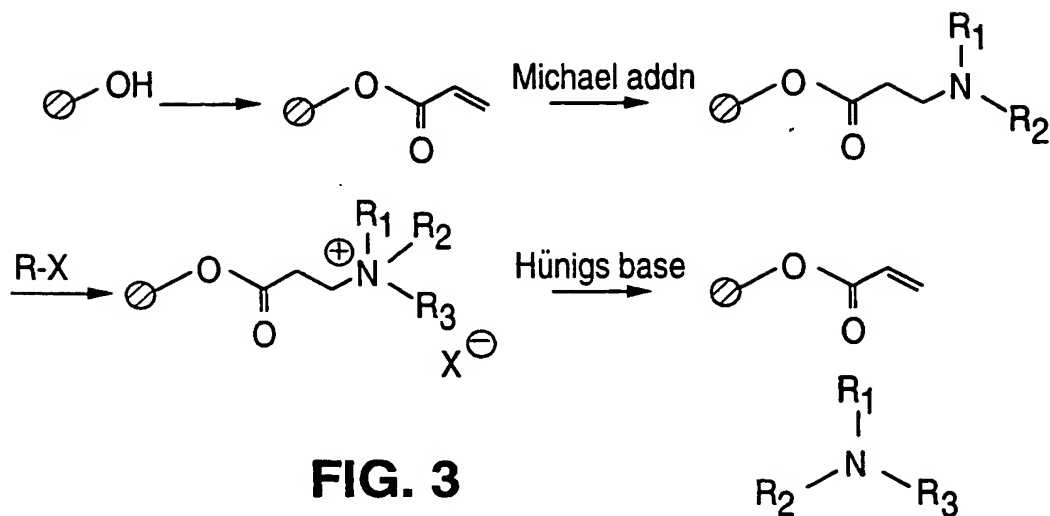


FIG. 3

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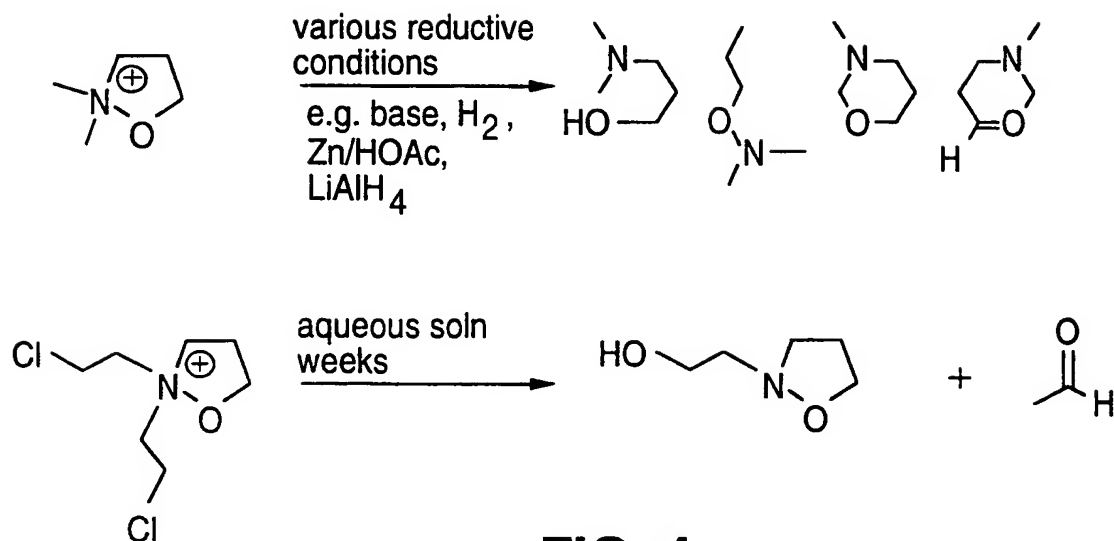


FIG. 4

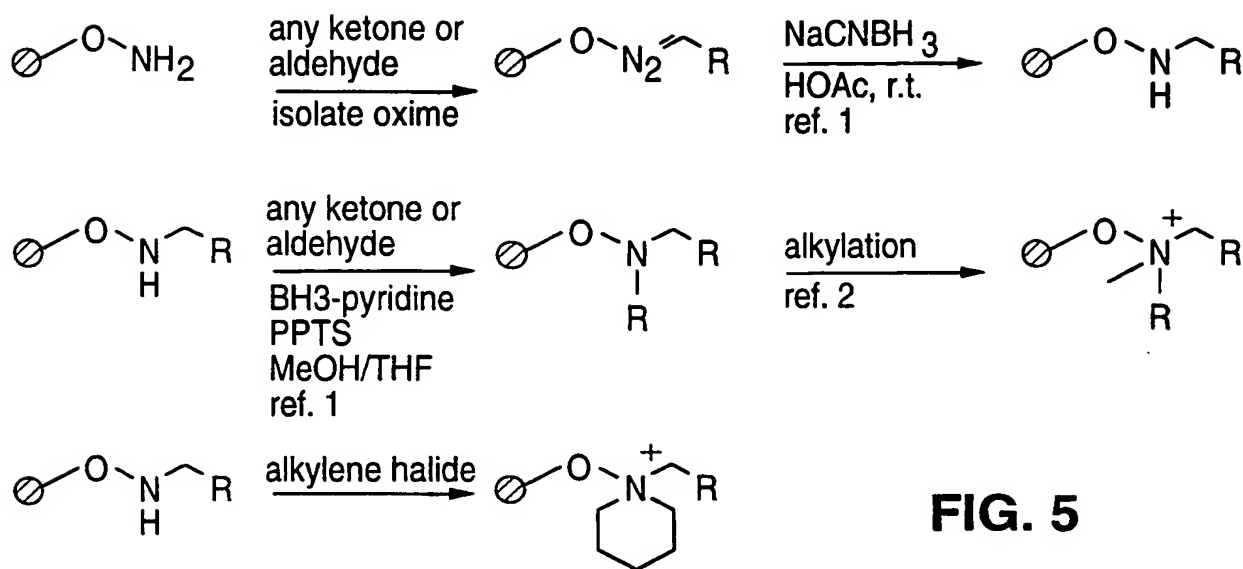


FIG. 5

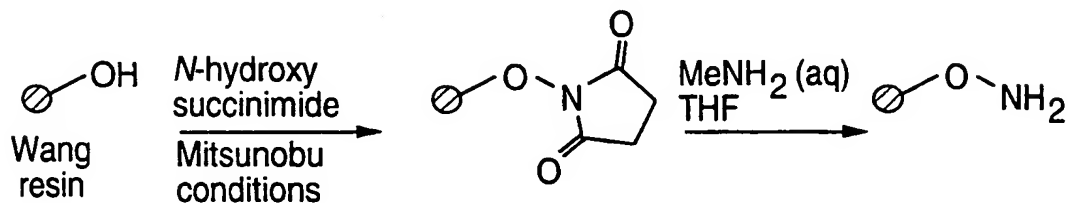


FIG. 6

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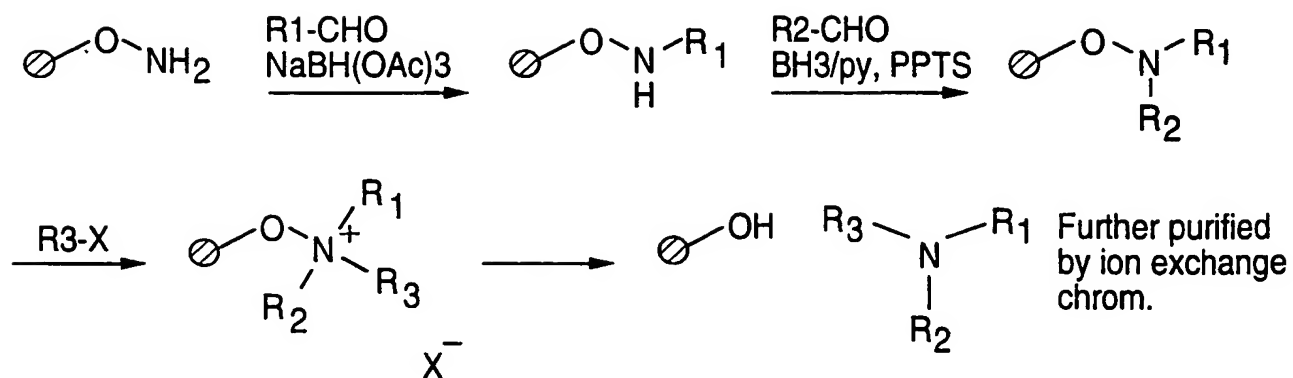


FIG. 7

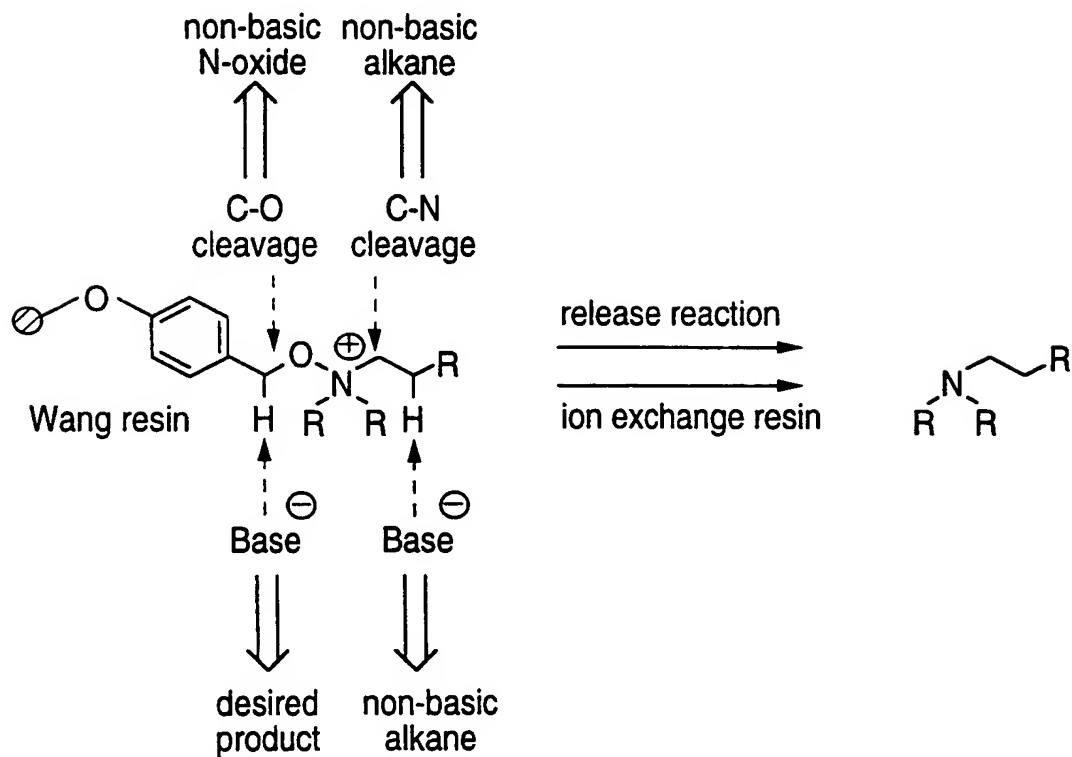


FIG. 8

INTERNATIONAL SEARCH REPORT

Interr. nal Application No

PCT/US 00/21225

A. CLASSIFICATION OF SUBJECT MATTER

IPC 7 C07C209/40 C07B61/00 C07C213/02 C07C213/08 C07C249/08

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

IPC 7 C07C C07B

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, CHEM ABS Data, BEILSTEIN Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 99 09073 A (AKZO NOBEL) 25 February 1999 (1999-02-25) claims 1,10; examples ---	1,19
A	WO 98 29376 A (RHONE-POULENC RORER) 9 July 1998 (1998-07-09) page 8, line 21 -page 9, line 15; claims 40-45 --- -/--	1,19

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

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Date of the actual completion of the international search

9 November 2000

Date of mailing of the international search report

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Zervas, B

INTERNATIONAL SEARCH REPORT

International Application No

PCT/US 00/21225

C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>JOSEPH M. SALVINO ET AL.: "Parallel Synthesis of Aldehydes and Ketone Facilitated by a New Solid-Phase Weinreb Amide" JOURNAL OF ORGANIC CHEMISTRY., vol. 64, no. 6, 19 March 1999 (1999-03-19), pages 1823-1830, XP002152402 AMERICAN CHEMICAL SOCIETY. EASTON., US ISSN: 0022-3263 cited in the application page 1824, column 1, line 1 -page 1827, column 2, line 26</p> <p style="text-align: center;">---</p>	1,19
A	<p>ANGELO LIGUORI ET AL.: "Novel Approach to the Ring-Opening Reaction of Isoxazolidinium Salts to 1,3-Amino Alcohols" CHEMISCHE BERICHTE, vol. 121, 1988, pages 105-109, XP002152403 WEINHEIM DE cited in the application page 105, column 1, line 1 -page 106, column 2, line 18</p> <p style="text-align: center;">---</p>	1,19
A	<p>ERIC E. SWAYZE ET AL.: "The Synthesis of N,N'-O-Trisubstituted Hydroxylamines via a Mild Reductive Alkylation Procedure: An Improved Synthesis of the MMI Backbone" SYNLETT., no. 7, July 1997 (1997-07), pages 859-861, XP002152404 THIEME VERLAG, STUTTGART., DE ISSN: 0936-5214 cited in the application the whole document</p> <p style="text-align: center;">-----</p>	1,19

INTERNATIONAL SEARCH REPORT

Information on patent family members

Interr. 1al Application No

PCT/US 00/21225

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